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(71) Applicant *(for all designated States except US)*: CHEMVET (NZ) LIMITED [NZ/NZ]; 208 North Karameu Road, Hastings 4201 (NZ).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: GRANT, Murray, Graham [NZ/AU]; 9 Whatton Place, Yea, VIC 3717 (AU).

(74) Agents: JACKSON, Timothy, Graham et al.; Russell McVeagh West-Walker, The Todd Building, Level 5, 171–177 Lambton Quay, Wellington 6001 (NZ).

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(54) Title: ANTHELMINTIC FORMULATION

(57) Abstract

The invention is directed to stable aqueous anthelmintic composition comprising an anthelmintic compound, an inorganic selenium salt, a stabilising amount of a primary organic solvent, a surface active agent, a co-solvent, a substrate, and a buffering system.

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ANTHELMINTIC FORMULATION

FIELD OF THE INVENTION

The invention is directed to a stable selenised anthelmintic composition which contains an inorganic selenium salt. The invention is also directed to a method by which such a formulation can be produced.

BACKGROUND OF THE INVENTION

Mineral deficiencies in soils and pastures are known to be detrimental to animal health. Selenium is an essential element and selenium deficiency in the diet is associated with a number of ailments such as muscular dystrophy, unthriftyness and infertility in female animals. Its exact metabolic function is however uncertain.

Anthelmintic compounds such as the avermectin and milbemycin series of compounds are well known and are useful for the treatment of helminthiasis amongst other ailments. The term "helminthiasis" encompasses diseases of animals caused by the infestation with parasitic worms such as strongyles, asciadis, hook worms, lung worms, filarial worms and whip worms. In addition the avermectins and milbemycins are active against Arthropods such as flies, lice, bugs, beetles and fleas and Arachnids, such as mites and ticks.

It has been noted that the addition of inorganic selenium salt to avermectin or milbemycin compositions appears to reduce the stability of the such compositions. It is thought that inorganic selenium salts have a catalytic-like or oxidative effect on the formulation which reduces the viability of the anthelmintic over time. Documents such as published New Zealand Patent Application No. 250188 to Ashmont Holdings Ltd, clearly refer to such instability. The extent of this instability is not clear, however, as there are selenised anthelmintic products currently on the market which combine sodium selenate and moxidectin, for example.

It is therefore an object of the invention to provide a stable aqueous anthelmintic composition which contains an inorganic selenium salt, or at least to provide the public with a suitable alternative of acceptable stability.

STATEMENT OF THE INVENTION

The invention in a first aspect is directed to a stable aqueous anthelmintic composition comprising an anthelmintic compound, an inorganic selenium salt, a stabilising amount of a primary organic solvent, a surface active agent, a co-solvent, a substrate and a buffering system.

Preferably the anthelmintic compound is selected from the avermectin or milbemycin series of compounds.

Preferably the anthelmintic compound is present in an amount, by weight of the composition, of between about 0.1 and about 5.0 g/l and more preferably between about 0.8 and about 2.5 g/l.

Preferably the anthelmintic compound is selected from ivermectin, abamectin, moxidectin or doromectin.

Preferably the primary organic solvent is present in an amount, by weight of the composition, of between about 3.0 and about 15%, more preferably between about 3.0 and about 10% and most preferably about 5%.

Preferably the primary organic solvent is glycerol formal propylene glycol methanol, benzyl alcohol, butyl diicinol, isopropanol, or mixtures thereof.

Preferably the inorganic selenium salt is sodium selenate or sodium selenite.

Preferably the composition contains between 0.2 and about 2.0 mg, and more preferably between about 0.2 and about 1.0 mg, of selenium per ml of the final solution. Most preferably the composition contains about 0.4 mg/ml selenium.

Preferably the surface active agent is polyoxyethylene sorbitan monooleate, polyoxyethylated vegetable oils, polyoxyethylene sorbitan monoisostearate, or polyoxyethylene

sorbitan monostearate or mixtures thereof.

Preferably the surface active agent is present in an amount, by weight, of between about 4.0 and about 18.0%, more preferably between about 7.0 and about 9.0% and most preferably about 8.0% of the composition.

Preferably the co-solvent is propylene glycol, glycerol formal, glycerine, or polyethylene glycol or mixtures thereof.

Preferably the co-solvent is present in an amount, by weight, of between about 15.0 and 30%, more preferably between 15 and 25% and most preferably 20%, of the composition.

Preferably the substrate is benzyl alcohol, lidocaine, parabens (i.e. esters of p-hydroxybenzoic acid), choline or mixtures thereof.

Preferably the substrate is present in an amount, by weight, of between about 1 and about 5% and more preferably between about 2.0 and about 4.0% and most preferably about 3% of the composition.

Preferably the buffering system comprises a mixture of dibasic and monobasic sodium phosphate.

Preferably the buffering system is present in an amount, by weight, of between about 0.1 and 2.0% and more preferably about 1.0%, of the composition.

Preferaly the pH of the composition is between about 6.0 and about 6.5. More preferably the pH is about 6.2.

Preferably the composition includes additional mineral supplements.

Preferably the additional mineral supplements include Zn, Co, Cu, Mn or I, supplements

and mixtures thereof.

The invention in a second aspect comprises a method for preparing a stable aqueous selenised anthelmintic composition comprising the following steps:

(a) dissolving the anthelmintic compound in a stabilising amount of a primary organic solvent;
(b) adding a surface active agent;
(c) adding a co-solvent;
(d) adding a substrate;
(e) adding a buffering system;
(f) adding water; and then
(g) adding an inorganic selenium salt.

Preferably the primary organic solvent is glycerol formal or propylene glycol.

Preferably the anthelmintic is an avermectin or milbemycin compound.

Preferably the surface active agent is polyoxyethylene sorbitan monooleate, polyoxyethylated vegetable oils, polyoxyethylene sorbitan monoisostearate, or polyoxyethylene sorbitan monostearate or mixtures thereof.

Preferably the co-solvent is propylene glycol, glycerol formal, glycerine, or polyethylene glycol or mixtures thereof.

Preferably the substrate is benzyl alcohol, lidocaine, parabens (i.e. esters of p-hydroxybenzoic acid), choline or mixtures thereof.

Preferably the buffering system is a phosphate buffer which comprises dibasic sodium phosphate and monobasic sodium phosphate.

Preferably the inorganic selenium salt is added in aqueous form.

Preferably the inorganic selenium salt is added together with ac
supplements.

Preferably the additional mineral supplements include Zn, Co, Cu, or I supplements or mixtures thereof.

The invention, in a third aspect, comprises a method of preparing a stable selenised anthelmintic composition having a pH between about 6.0 and about 6.5, the method comprising the following steps (all % by weight):

(a) dissolving an avermectin or milbemycin compound in between about 3.0% and about 15%, of glycerol formal and/or propylene glycol;
(b) adding between about 4.0% and about 18% of a surface active agent;
(c) adding between about 15% and about 30% of a co-solvent;
(d) adding between about 1.0% and about 5.0% of a substrate;
(e) adding between about 0.1% and about 2% of a phosphate buffer; then
(f) adding water (q.s.); then
(g) adding, to the solution formed by steps (a) to (f), an aqueous solution of sodium selenate or sodium selenite containing sufficient selenium to result in between about 0.2 and about 1.0mg of selenium per ml of the final composition.

The preferred component amounts referred to in this specification and claims may be any figure, or range of figures, falling within the respective percentage ranges of the components referred to.

DETAILED DESCRIPTION OF THE INVENTION

This invention is directed to a stable aqueous anthelmintic formulation containing an inorganic selenium salt and to a method for manufacturing such a formulation.

The addition of inorganic selenium to formulations containing anthelmintics such as the

avermectins and milbemycins, usually leads to a lack of stability in the formulation. This is thought to be due to the selenium having a catalytic-type effect on the degradation of the anthelmintic active compound. In other words, the inorganic selenium hastens the break down of the anthelmintic compound over time thus reducing its viability. While it is possible to mix inorganic selenium, in the form of a drench for example, with an anthelmintic formulation just prior to application to the animal, there is an obvious advantage in being able to provide a combined inorganic selenium/anthelmintic formulation with sufficient stability for long term storage. This would allow for single formulation storage and single dose administration.

As stated previously herein, the reasons for, and the extent of, this instability, are unclear. It is possible that factors such as pH or storage temperature, or both, may contribute to the stability or otherwise of avermectins and milbemycins in the presence of inorganic selenium salts. In any event, there is a perceived difficulty in relation to selenised anthelmintic products containing avermectins or milbemycins, which surrounds the stability of these products over time.

The composition and method of the present invention provides a stable combination of anthelmintic compounds, such as the avermectins and milbemycins, with inorganic selenium salts. It is thought that the stability of the composition, to which the present invention is directed, is due to the high proportion of organic solvents present in the composition. The specific method by which the composition is manufactured, as discussed later in this description, allows the formation of a protective layer of organic compound around the anthelmintic compound, thus protecting it from the onset of degradation which is hastened by the inorganic selenium salt.

The primary organic solvent for the anthelmintic compound is preferably glycerol formal, however, propylene glycol may also be used. Other suitable compounds, such as methanol, benzyl alcohol, butyl diicinol or isopropanol, or mixtures thereof, may also be used as will be known in the art. The amount of the primary organic solvent in the composition is preferably between about 3 and about 15%, more preferably between about 4 and about 10%, by weight, with the most preferred amount being about 5%.

The composition also includes a surface active agent such as polyoxyethylene sorbitan monooleate, polyoxyethylated vegetable oils, polyoxyethylene sorbitan monoisostearate, or polyoxyethylene sorbitan monostearate or mixtures thereof. The surface active agent is preferably present in the composition in an amount, by weight of the composition, of between about 4.0 and about 18%, more preferably between about 7.0 and about 15% more preferably between 7.0 and 9.0% and most preferably about 8.0%.

The co-solvent is preferably selected from compounds including propylene glycol, glycerol formal, glycerine, polyethylene glycol or mixtures thereof. The co-solvent is preferably present in an amount by weight of between about 15 and about 30%, more preferably between 15 and 25% and most preferably about 20% by weight of the composition.

The substrate may be selected from compounds including benzyl alcohol, lidocaine, parabens, (i.e. esters of p-hydroxybenzoic acid), or choline or mixtures thereof. The substrate may preferably be present in an amount by weight of between about 1 and 5% and more preferably about 3%.

Any percentage figure that falls within the ranges specified for the components of the composition may be used as will be clear to a skilled person. The lists of preferred compounds of use as the primary organic solvent, the surface active agent, the co-solvent and the substrate are not intended to be limiting. Any suitable compounds as will be known to a skilled person may be used.

The method of preparing the composition of the present invention results in a formulation containing micelles comprising the anthelmintic compound surrounded by the primary organic solvent (e.g. glycerol formal), the co-solvent and the substrate. It is thought that the surface active agent allows the mixture formed by the anthelmintic/solvent combination, as described previously, to solubilise in the co-solvent and/or then encourage the total mixture to form micelles in the water base or aqueous phase. Therefore the combination of the level of solvent, co-solvent and substrate appears to allow enough protection of the active constituents to ensure protection from degradation even in the presence of the inorganic selenium salt used, which presumably

remains in the aqueous phase of the solution.

A preferred method of producing the composition of the present invention comprises:

(a) dissolving the anthelmintic compound in the primary organic solvent (e.g. glycerol formal);
(b) adding a suitable surfactant compound such as polyoxyethylene sorbitan mono oleate;
(c) adding the co-solvent (e.g. propylene glycol);
(d) adding a suitable substrate compound such as benzyl alcohol;
(e) buffering the composition;
(f) adding water; then
(g) adding the inorganic selenium salt.

The composition is preferably buffered with a phosphate buffer which preferably comprises a mixture of dibasic sodium phosphate and monobasic sodium phosphate. Alternative buffering systems as will be known in the art may also be used. The buffer system is preferably in an amount of about 1.0% by weight of the composition. This amount may vary however as will be known in the art. The amount may therefore be between about 0.1 and about 2.0% for example. The buffer system used preferably maintains the pH of the composition between about 6.0 and about 6.5, preferably about 6.2.

The selenium is preferably added as a aqueous solution sufficient to provide an amount between about 0.2 and about 1.0 mg of selenium per ml in the final composition. An amount of about 0.4 mg per ml is preferred. The aqueous solution can be prepared by any suitable manner as will be known to a person skilled in the art. The inorganic selenium salts used can be in any form as will be known to a skilled person. The preferred inorganic selenium salts being sodium selenite and sodium selenate.

It has also been found that the anthelmintic and inorganic selenium containing composition is stable after the addition of other mineral compounds (eg iodine, copper,

zinc, manganese and cobalt) which are useful for the treatment and prevention of mineral deficiencies in livestock. The composition can thus provide a stable multi-treatment option for treatment of mineral deficiencies, including selenium deficiency, while at the same time providing an effective anthelmintic treatment. Other mineral supplements as will be known in the art can also be included in the formulation. The additional mineral supplements can be added to the formulation in any suitable form such as, but not limited to, the EDTA salts of zinc, copper and cobalt, and alkyl diamine (eg ethyl diamine) salts of iodine. Other known chelate salts of these compounds may also be used as will be known in the art.

EXAMPLES

Example 1

FORMULATION TYPE

An aqueous oral drench for sheep containing 0.8 gm/litre (w/v) abamectin.

COMPOSITION

Abamectin	0.8 gm/l
Propane-1,2-diol	200 gm/l
Glycerol formal	50 gm/l
Polyoxethylene Sorbitan monooelate (Polysorbate 80)	80 gm/l
Benzyl alcohol	30 gm/l
Sodium Phosphate Dibasic anhydrous	1.0 gm/l
Sodium Phosphate Monobasic	9.0 gm/l
Water Pyrogen Free	to volume

PHYSICAL AND CHEMICAL CHARACTERISTICS

Colourless to slightly amber Aqueous Micelle Solution

pH 6.0-6.2

Specific Gravity 1.04 g/ml

Example 2

The following summarises the method for the manufacture of 2000 litres of product excluding the selenium content;

1) Measure 100 kg Glycerol Formal into dedicated, appropriately cleaned, HDPE mixing tank.

2) Add, with constant stirring, 1632 gms Abamectin. Continue stirring until the Abamectin is completely dissolved.

3) Add 160 kg Tween 80 slowly with constant swirling mixing to obtain homogeneity.

4) Add 400 kg Propylene Glycol slowly with constant swirling. Continue to obtain homogeneity.

5) Add 60 kgm Benzyl Alcohol and swirl to obtain homogeneity.

6) Add 2 kgm anhydrous dibasic sodium phosphate and 18 kg, of monobasic sodium phosphate monohydrate and disperse in the mixture.

7) Slowly with gentle swirling add 800 litres of treated process water until the phosphates have dissolved in the solution.

8) Add treated process water to the 2000 level and continue mixing gently until a homogenous mixture is obtained.

9) Once fully mixed and successfully assayed to specification, the product will be pumped from the tank, via demountable and suitably cleansed stainless steel pipework, through a service duct in the wall to the filling area. The pump used was a polypropylene bodied magnetically driven centrifugal pump.

Example 3 - Selenium Additive

An aqueous solution of sodium selenite 50 mg/mL equivalent to 22.5 mg/mL selenium may be used as a selenium additive.

Selenium Drench Content (Aqueous)

%	Se	=	45.47
%	NaSe03	=	99.60
%	NaSe04	=	0.05
	Te	=	2 ppm
	Cr	=	< 1 ppm
	Zn	=	5 ppm
	Sb	=	3 ppm
	Pb	=	2 ppm
	Co	=	< 1 ppm
	Al	=	2 ppm
	Cu	=	2 ppm
	Fe	=	4 ppm
	Cd	=	< 1 ppm
	As	=	< 1 ppm
	Ag	=	< 1 ppm
	Ba	=	< 1 ppm
	Hg	=	< 0.05 ppm

Example 4 - Selenised Anthelmintic Drench

A mix of the compositions is then prepared by the addition of the aqueous Selenium solution of Example 3 to the already formulated Abamectin composition of Example 1 to produce a solution containing 0.4 mg selenium/ml.

Stability of Combination

Stability analyses of the combination of Example 4 were carried out at 37°C over the following intervals:

1, 2, 3, 4, 6, 8, 12, 16, 24, 36 and 48 weeks.

The Abamectin analyses were conducted using standard HPLC methods for the analysis of Abamectin.

The selenium analyses were conducted using standard Atomic Absorption Spectrographic method for the analysis of selenium in anthelmintic formulations.

RESULTS

Week	Abamectin (g/l)	Selenium (mg/mL)	Selenium as Sodium Selenite (mg/mL)
0	0.78	0.38	0.84
1	0.79	0.38	0.84
2	0.78	0.37	0.82
3	0.78	0.37	0.82
4	0.78	0.38	0.83
6	0.77	0.36	0.8
8	0.78	0.38	0.83
12	0.78	0.38	0.83
16	0.78	0.37	0.81
24	0.77	0.37	0.82
36	0.77	0.37	0.82
48	0.77	0.38	0.83

CONCLUSION

The results of this accelerated stability study adequately demonstrates the stability of the anthelmintic drench following the addition of selenium, in the form of an inorganic selenium salt. The results clearly indicate no degradation of the anthelmintic used after 48 weeks accelerated storage at 37°C.

Example 5

Preparation and testing of "Rycomectin LV (abamectin low volume) + Selenium", prepared as follows:

Glycerol formal:	100 g
Abamectin:	2.0 g
Tween 80:	100 g
Propylene glycol:	240 g
Benzyl alcohol:	36 g
Sodium phosphate dibasic, anhydrous:	1.2 g
Sodium phosphate monobasic, mononydrate:	10.8 g
Selenium (as sodium selenate):	1.0 g
Water:	to 1 litre

Assay:

Abamectin:	1.9 g/L
Selenium:	0.97 g/L
As sodium selenate:	2.32 g/L

The formulation was prepared as per the method disclosed in Examples 2 and 3 with the necessary component amount adjustments.

Results of Stability Study (37°C)

Abamectin Low Volume Formulation

Week	Abamectin g/L	Selenium mg/mL	Selenium as sodium selenate mg/mL
0	1.9	0.97	2.32
2	1.9	0.98	2.33
4	1.9	0.97	2.32
8	1.9	0.99	2.37
26	1.9	0.96	2.30

The analysis were conducted using instrumentation as for Example 4.

Example 6

Stability of Formulation on Addition of Minerals

The formulation of the present invention has been found to be stable after the addition of other mineral compounds, such as iodine, copper, zinc and cobalt, useful for the treatment and prevention of mineral deficiencies in livestock.

A stability study "A" was performed as for previous Examples. In the same manner as the addition of selenium described in Examples 2 and 3, the following minerals were added to the formulation:

Selenium as selenium selenate

Zinc as zinc EDTA

Copper as copper EDTA

Cobalt as cobalt EDTA

Iodine as EDDI

Concurrently a second stability study "B" was conducted with the addition of the same combination of minerals accept the selenium which was in the form of selenium selenite. The composition of the zinc, copper, cobalt, and iodine components are detailed in Tables I to IV.

TABLE I - COBALT

PRODUCT NAME	:	LIBREL Co
CHEMICAL DESCRIPTION	:	Cobalt disodium ethylenediamine tetraacetate (CoEDTA)
MOLECULAR FORMULA	:	$C_{10} H_{12} N_2 O_8 Na_2 Co$
MOLECULAR WEIGHT	:	393
TYPICAL ANALYSIS	:	Cobalt (as Co) 14.0%
PHYSICAL APPEARANCE	:	Deep pink powder
SOLUBILITY (in water)	:	280 gl^{-1} (at 20°C)

TABLE II - COPPER

PRODUCT NAME	:	LIBREL Cu
CHEMICAL DESCRIPTION	:	Copper disodium ethylenediamine tetraacetate (CuEDTA)
MOLECULAR FORMULA	:	$C_{10} H_{12} N_2 O_8 Na_2 Cu$
MOLECULAR WEIGHT	:	397
TYPICAL ANALYSIS	:	Copper (as Cu) 14.0%
PHYSICAL APPEARANCE	:	Blue powder
SOLUBILITY (in water)	:	357 gl^{-1} (at 20°C)

TABLE III - ZINC

PRODUCT NAME	:	LIBREL Zn
CHEMICAL DESCRIPTION	:	Zinc disodium ethylenediamine tetraacetate (ZnEDTA)
MOLECULAR FORMULA	:	$C_{10}\ H_{12}\ N_2\ O_8\ Na_2\ Zn$
MOLECULAR WEIGHT	:	399
TYPICAL ANALYSIS	:	Zinc (as Zn) 14.0%
PHYSICAL APPEARANCE	:	Off-white granule
SOLUBILITY (in water)	:	300 gl^{-1} (at 20°C)

TABLE IV - IODINE

ETHYLENE DIAMINE DIHYDRIODIDE

SYNONYMS: EDDI

CHEMICAL FORMULA: $(H_2NCH_2CH_3NH_2)$ - 2HI

Molecular Weight	315.92	
Iodine (I)		80.3%
Azote (N)		8.9%
Carbon (C)	7.6%	

DESCRIPTION: White to slightly yellowish, free-flowing crystals, consisting of essentially pure ethylene diamine dihydriodide.

PHYSICAL PROPERTIES: Solubility: Very soluble in water.
120 g dissolves in 100 g water at 25°C.

CHEMICAL SPECIFICATIONS

TEST	LIMITS	TYPICAL
E.D.D.I.	Minimum 98.0%	99.0 - 99.7%
Iodine	Minimum 78.7%	79.5 - 80.1%
pH (10% solution)	3.5 - 5.5	4.0 - 5.0
Insoluble matters	Maximum 0.5%	0.25%

Result: Mineralised Stability Study 48 Weeks Accelerated (37°C)

"A" Selenium as sodium selenate

Week	Abamectin g/L	Cobalt mg/mL	Copper mg/mL	Zinc mg/mL	Selenium mg/mL	Iodine mg/mL
0	0.80	0.13	1.44	0.35	0.39	0.81
4	0.80	0.13	1.44	0.35	0.40	0.80
8	0.80	0.14	1.44	0.34	0.39	0.79
17	0.80	0.14	1.44	0.35	0.37	0.77
22	0.78	0.14	1.45	0.34	0.37	0.80
48	0.79	0.14	1.46	0.35	0.37	0.78

"B" Selenium as sodium selenite

Week	Abamectin g/L	Cobalt mg/mL	Copper mg/mL	Zinc mg/mL	Selenium mg/mL	Iodine mg/mL
0	0.79	0.13	1.44	0.35	0.39	0.82
4	0.80	0.13	1.44	0.35	0.40	0.81
8	0.80	0.14	1.44	0.34	0.39	0.80
17	0.80	0.14	1.45	0.35	0.37	0.78
22	0.78	0.13	1.45	0.34	0.38	0.78
48	0.79	0.14	1.46	0.34	0.37	0.78

The studies demonstrate the surprising stability through to 48 weeks (accelerated @ 37°C) of each formulation.

The stability results given in the Examples, under the accelerated conditions used, indicate that a shelf life in excess of 2 years for the compositions of the present invention, can be supported.

The foregoing describes the invention including preferred forms and examples thereof. Alterations and modifications as will be obvious to a person skilled in the art are intended to be included with the scope of the invention as defined in the appended claims.

CLAIMS:

1. A stable aqueous anthelmintic composition comprising an anthelmintic compound, an inorganic selenium salt, a stabilising amount of a primary organic solvent, a surface active agent, a co-solvent, a substrate, and a buffering system.

2. The composition of claim 1 wherein the anthelmintic compound is selected from the avermectin or milbemycin series of compounds.

3. The composition of claim 1 or claim 2 wherein the anthelmintic compound is selected from ivermectin, abamectin, moxidectin, or doromectin.

4. The composition of any one of the previous claims wherein the primary organic solvent is present in an amount, by weight of the composition, of between about 3.0 and about 15%.

5. The composition according to claim 4 wherein the primary organic solvent is present in an amount of between about 3.0 and about 10%.

6. The composition according to claim 4 or claim 5 wherein the primary organic solvent is present in an amount of about 5% by weight of a composition.

7. The composition according to any one of the previous claims wherein the primary organic solvent is glycerol formal or propylene glycol or mixtures thereof.

8. The composition according to any one of the previous claims wherein the inorganic selenium salt is sodium selenate or sodium selenite.

9. The composition according to any one of the previous claims wherein the composition contains between about 0.2 and about 1.0 mg of selenium per ml of the composition.

10. The composition according to claim 9 wherein the composition contains about 0.4 mg selenium per ml of the final composition.

11. The composition according to any one of the previous claims wherein the surface active agent is selected from the group consisting of polyoxyethylene sorbitan monooleate, polyoxyethylated vegetable oils, polyoxyethylene sorbitan monoisostearate, or polyoxyethylene sorbitan monostearate, or mixtures thereof.

12. The composition according to any one of the previous claims wherein the surface active agent is present in an amount, by weight of the composition, of between about 4.0 and 18.0%.

13. The composition according to claim 12 wherein the surface active agent is present in an amount of about 8.0% by weight of the composition.

14. The composition according to any one of the previous claims wherein the co-solvent is selected from the group consisting of propylene glycol, glycerol formal, glycerine, or polyethylene glycol, or mixtures thereof.

15. The composition according to any one of the previous claims wherein the co-solvent is present in an amount, by weight of the composition, of between about 15.0 and 30%.

16. The composition according to claim 15 wherein the co-solvent is present in an amount, by weight of the composition, of about 20%.

17. The composition according to any one of the previous claims wherein the substrate is selected from the group consisting of benzyl alcohol, lidocaine, parabens, choline, or mixtures thereof.

18. The composition according to any one of the previous claims wherein the substrate is present in an amount, by weight of the composition, of between about 1.0 and about 5%.

19. The composition according to claim 18 wherein the substrate is present in an amount, by weight of the composition, of about 3%.

20. The composition according to any one of the previous claims wherein the buffering system comprises a mixture of dibasic and monobasic sodium phosphate.

19. The composition according to claim 18 wherein the substrate is present in an amount, by weight of the composition, of about 3%.

20. The composition according to any one of the previous claims wherein the buffering system comprises a mixture of dibasic and monobasic sodium phosphate.

21. The composition according to any one of the previous claims wherein the buffering system is present in an amount, by weight of the composition, of between about 0.1 and 2.0%.

22. The composition according to claim 21 wherein the buffering system is present in an amount, by weight of the composition, of about 1.0%.

23. The composition according to any one of the previous claims wherein the pH is between about 6.0 and about 6.5.

24. The composition according to any one of the previous claims wherein the composition further comprises mineral supplements additional to selenium.

25. The composition according to claim 24 wherein the additional mineral supplements are selected from zinc, cobalt, copper, and manganese iodine supplements and mixtures thereof.

26. A method for preparing a stable aqueous selenised anthelmintic composition comprising the following steps:

(a) dissolving the anthelmintic compound in a stabilising amount of a primary organic solvent;
(b) adding a surface active agent;
(c) adding a co-solvent;
(d) adding a substrate;
(e) adding a buffering system;
(f) adding water; and then

(g) adding an inorganic selenium salt.

27. The method according to claim 26 wherein the primary organic solvent is selected from glycerol formal, propylene glycol, methanol, benzyl alcohol, butyl diicinol, isopropanol, or mixtures thereof.

28. The method according to claim 26 or claim 27 wherein the anthelmintic compound is selected from the avermectin or milbemycin group of compounds.

29. The method according to any one of claims 26 to 28 wherein the surface active agent is selected from the group of compounds consisting of polyoxyethylene sorbitan monooleate, poly-oxyethylated vegetable oils, polyoxyethylene sorbitan monoisostearate, or polyoxyethylene sorbitan monostearate or mixtures thereof.

30. The method according to any one of claims 26 to 29 wherein the co-solvent is selected from the group of compounds consisting of propylene glycol, glycerol formal, glycerine, or polyethylene glycol or mixtures thereof.

31. The method according to any one of claims 26 to 30 wherein the substrate is selected from the group of compounds selected from benzyl alcohol, lidocaine, parabens, choline or mixtures thereof.

32. The method according to any one of claims 26 to 31 wherein the buffering system is a phosphate buffer which comprises dibasic sodium phosphate and monobasic sodium phosphate.

33. The method according to any one of claims 26 to 32 wherein the inorganic selenium salt is added in aqueous form.

34. The method according to any one of claims 26 to 33 wherein the inorganic selenium salt is added together with additional mineral supplements.

35. The method according to claim 34 wherein the additional mineral supplements include Zn, Co, Cu, Mn and I supplements, or mixtures thereof.

36. A method of preparing a stable selenised anthelmintic composition having a pH between about 6.0 and about 6.5 comprising the following steps (all amounts by weight):

(a) dissolving an avermectin or milbemycin compound in between about 3.0% and about 15%, of glycerol formal and/or propylene glycol;
(b) adding between about 4.0% and about 18% of a surface active agent;
(c) adding between about 15% and about 30% of a co-solvent;
(d) adding between about 1.0% and about 5.0% of a substrate;
(e) adding between about 0.1% and about 2.0% of a phosphate buffer; then
(f) adding water (q.s.); then
(g) adding, to the solution formed by steps (a) to (f), an aqueous solution of sodium selenate or sodium selenite which contains sufficient selenium to result in between about 0.2 and about 1.0 mg of selenium per ml of the final composition.

37. The method of any one of claims 26 to 36 wherein the pH of the composition formed is about 6.2.

38. A stable aqueous selenised anthelmintic composition substantially as herein described with particular reference to any one of the Examples.

39. A method of preparing a stable aqueous selenised anthelmintic composition substantially as herein described with reference to any one of the Examples.

INTERNATIONAL SEARCH REPORT

International Application No.
PCT/NZ 97/00141

A. CLASSIFICATION OF SUBJECT MATTER

Int Cl[6]: A61K 031/35; A61K 033/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC: A61K, A01N, Search Terms as below

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
AU: IPC as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
DERWENT WPAT; (Se or Selen:) AND (Milbemycin # or Avermectin # or Ivermectin # or Abamectin # or
C.A. (STN): Moxidectin # or Doromectin # or Anthelmintic: or Helminth: or Nematode: or Worm:)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB 2 283 677 A (Ashmont Holdings Limited) 17 May 1995 Whole document especially the claims	1-39
X	GB 2 213 722 A (Ancare Distributors Limited) 23 August 1989 Whole document	1, 4-39
X	GB 2 117 241 A (Hoechst UK Limited) 12 October 1983 Whole document especially the claims	1, 4-39

☐ Further documents are listed in the continuation of Box C

☒ See patent family annex

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search
22 January 1998

Date of mailing of the international search report
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Name and mailing address of the ISA/AU
AUSTRALIAN INDUSTRIAL PROPERTY ORGANISATION
PO BOX 200
WODEN ACT 2606
AUSTRALIA Facsimile No.: (02) 6285 3929

Authorized officer
T. SUMMERS
Telephone No.: (02) 6283 2291

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INTERNATIONAL SEARCH REPORT
Information on patent family members

International Application No.
PCT/NZ 97/00141

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member					
GB	2 283 677	AU	77717/94				
GB	2 117 241	AU	12966/83	DE	3373276	EP	90368
GB	2 213 722	AU	27505/88				

END OF ANNEX